

*THE INTERSECTION OF CUTTING-EDGE SOCIAL,
BEHAVIORAL AND BIOMEDICAL STRATEGIES
FOR HIV PREVENTION*

Symposium Proceedings

An affiliated meeting of the XVI International AIDS Conference,
Toronto, Canada
August 12, 2006

Sponsored by the Center for HIV Identification, Prevention, and Treatment
Services (CHIPTS) and the UCLA AIDS Institute

June 2007

THE INTERSECTION OF CUTTING-EDGE SOCIAL, BEHAVIORAL AND
BIOMEDICAL STRATEGIES FOR HIV PREVENTION

TABLE OF CONTENTS

Introduction	4
Symposium Overview	4
Presentations	
Welcoming Remarks	
<i>Mary Jane Rotheram-Borus, Ph.D.</i>	
<i>Andrew Forsyth, Ph.D.</i>	6
Panel Session #1: Microbicides	
Microbicides –	
<i>Ian McGowan, M.D.</i>	8
Microbicide Acceptability and Adherence –	
<i>Alex Carballo-Dieiguez, Ph.D.</i>	10
Panel Session #2: Pre-Exposure Prophylaxis	
The Iniciativa PrEx Study: Safety, Efficacy, Behavior, and Biology –	
<i>Robert M. Grant, M.D., M.P.H.</i>	13
Assessing Community and Investigators Needs for Successful Trial Implementation –	
<i>Pedro Goicochea, MSc, MA</i>	15
Panel Session #3: Male Circumcision	
Male Circumcision: A Prevention Method Against HIV in South Africa –	
<i>Bertran Auvert, M.D., Ph.D.</i>	17
Male Circumcision for HIV and STI Prevention in Men and Women –	
<i>Maria Wawer, M.D., M.H., S.c.</i>	19
Panel Session #4: Regional Mobilization	
HIV Prevention: Behavioral and Biomedical Interventions in the U.S. –	
<i>Kevin Fenton, M.D., Ph.D.</i>	24
HIV/AIDS: A Special Infectious Disease –	
<i>Zunyou Wu, M.D., Ph.D.</i>	26
Intersections of Socio-Behavioral Research and Biomedical Strategies for HIV Prevention in Tanzania –	
<i>Jessie Mbwambo, M.D.</i>	28
Recommendations	
Conducting Clinical Trials.....	31

Implementing Biomedical HIV Prevention Strategies.....	31
The Role of Social and Behavioral Scientists in Development and Implementation of Biomedical HIV Prevention Strategies.....	33
Participant List.....	33
References...	

Introduction

With an estimated 4 million new HIV infections occurring annually worldwide, the development of new, safe, effective, and accessible prevention methods is urgently needed (Global HIV Prevention Working Group, 2006). Several new biomedical strategies to advance HIV prevention are currently being studied (*i.e.*, microbicides, Pre-Exposure Prophylaxis, herpes suppression, and diaphragms) and preliminary evidence suggests the potential impact of each of these approaches in slowing the spread of HIV. Another biomedical strategy, adult male circumcision, was recently shown to be effective in reducing a man's risk of acquiring HIV through heterosexual intercourse by 51% to 53% (Sawires, et al., 2007). It is likely that within the next few years other biomedical methods will demonstrate efficacy and will be introduced for general use in community and clinical settings.

If ongoing studies of these biomedical prevention methods demonstrate the effectiveness of these approaches, these methods (used individually or in combination) may have a dramatic impact on controlling the HIV pandemic. In addition to efficacy, other factors make these prevention methods highly desirable. Some offer lifelong risk reduction (circumcision, vaccines). Other methods uniquely empower women to initiate HIV prevention (microbicides, diaphragm) or permit targeting to specific behavioral risk groups (PrEP).

To further curtail HIV transmission, domestic and international prevention efforts will need to incorporate biomedical approaches into their arsenal of prevention interventions. Implementation of these biomedical approaches will generate a new set of behavioral issues that will need to be addressed to ensure that the full benefit of an expanded prevention portfolio (*i.e.*, biomedical and behavioral strategies) is realized.

These proceedings summarize presentations by leading biomedical and social/behavioral researchers on the current state of biomedical HIV prevention strategies and key social and behavioral issues associated with their future implementation. The symposium, presented in conjunction with the XVI International AIDS Conference in 2006, examined three emerging biomedical prevention interventions (microbicides, PrEP and male circumcision) and initiated a discourse on the intersection of social, behavioral, and biomedical strategies in advancing these novel HIV prevention strategies globally.

Symposium Overview

Sponsors

The Center for HIV Identification, Prevention, and Treatment Services (CHIPTS), in partnership with the UCLA AIDS Institute convened this symposium entitled, "The Intersection of Cutting-Edge Social, Behavioral and Biomedical Strategies for HIV Prevention" in Toronto, Canada on August 12, 2006 prior to the start of the XVI International AIDS Conference. CHIPTS is supported by the National Institute of Mental Health.

Goal

To initiate a discourse among a multi-disciplinary group of stakeholders on the intersection of social, behavioral, and biomedical strategies in advancing HIV prevention efforts globally.

Objectives

- To identify the unique role social and behavioral science will play in improving the acceptability, accessibility, adherence, sustainability, and robustness of new biomedical strategies throughout the world.
- To identify the current state of emerging biomedical strategies for HIV prevention.
- To develop a policy statement on the future role of social and behavioral research in the adoption of new biomedical technologies for HIV prevention.
- To outline a research agenda for developing social and behavioral strategies to increase uptake of new biomedical approaches to HIV prevention.

Format

The symposium consisted of paired presentations by leaders in the biomedical, social, and behavioral fields who are working on new HIV prevention strategies. A facilitated group discussion followed each panel on the role of social and behavioral science in promoting the acceptability and adoption of new technologies. A lunchtime presentation looked at the regional mobilization of biomedical and behavioral interventions in the U.S., Asia and Africa.

Welcoming Remarks

Mary Jane Rotheram-Borus, Ph.D.

Director

Center for HIV Identification, Prevention, and Treatment Services

University of California, Los Angeles, USA

We welcome you today on behalf of both CHIPTS and our major partner, the AIDS Institute at UCLA, and we have Ned Baird here this morning who has been our collaborator in organizing today's symposium, to welcome you for a day of what we hope will be a day of exploration, creativity and hope. New technologies have created new possibilities of how our prevention agenda can shift and expand to combat HIV. Aristotle once said "the soul never thinks without a picture," and today what we are trying to focus on is to create and put some color and texture and vision to that picture of what the new prevention agenda can be. We are trying to focus on the intersection of social, behavioral and biomedical interventions, and today, in order to do that, we have a very broad cross-section of community-based agencies, clinical and behavioral researchers and providers, government representatives, foundation representatives, clinicians, persons with HIV, persons with AIDS, and we hope that in this intersection of people that bring very diverse perspectives to the table, we can begin to paint that picture and that vision for the new prevention agenda in a different way.

The typical relationship between behavioral researchers and biomedical researchers is that we have very different agendas and very different perspectives and very different needs, and it is sometimes difficult to communicate them. Today we are looking to cross that bridge.

Andrew D. Forsyth, Ph.D.

Prevention and Behavioral Research Branch

National Institute of Mental Health, Bethesda, USA

The goals of the symposium are to encourage 'out of the box' thinking about the intersection of behavioral, social and biomedical sciences, and their impact together as a strategy to prevent HIV. Several landmark trials in recent years have highlighted the need to explore the novel terrain in this area, and we are pleased at NIMH to have Mary Jane and her colleagues at UCLA take a leadership role in exploring these areas with us here today.

The June 2006 *MMWR* on the 25th anniversary of HIV in the US authored by Kevin Fenton and others at CDC made a critical point about adjusting our expectations about the new HIV prevention strategies and technologies that are in development and under testing currently, and these include, obviously, PrEP, microbicides, vaccines, and circumcision. In short, it reminded us that these advances are unlikely to provide full protection against HIV, that they may offer little or no protection against other STIs, and that they will provide no protection, likely, against unintended pregnancies. Now ultimately in order to fulfill their potential, these advances will need to be incorporated into a comprehensive HIV prevention strategy; one that takes into consideration, among

other dimensions, this intersection between the relevant behavioral, social and biomedical sciences. As we will hear very shortly today, the accumulating evidence suggests that we would be wise to remain vigilant of opportunities to include these advances into a comprehensive HIV prevention strategy in a manner that facilitates an overall risk avoidance and interferes minimally with the initiation and maintenance of behaviors that reduce new infections.

Panel Session #1: Microbicides

Microbicides

Ian McGowan, M.D.

Microbicide Development Program

David Geffen School of Medicine

University of California, Los Angeles, USA

Dr. McGowan provided a brief overview of the current state of microbicide science, including mucosal transmission of HIV infection, the microbicide pipeline, RT-inhibitor microbicides, combination microbicides, formulation science, rectal microbicide, and microbicide development and the community.

Highlights of Dr. McGowan's presentation:

Mucosal Transmission

Mucosal transmission is where it happens, so the object of microbicides is either to protect or at least offer substantial protection against transmission of HIV. Both the rectum and the endocervical canal are exceptionally sensitive to HIV transmission.

The approach for microbicide development is to think about strategies to prevent the virus from getting in, and even that process is affected by multiple pathways.

Because the virus and virus cell combination travel out of the mucosa quite quickly after infection, it is important to make sure that the product is around sufficiently to prevent the egress of infected cells and virus to regional lymph nodes.

Microbicide Pipeline

The approach for development of microbicides is to look at each of the different steps in transmission and develop products or compounds that actually interact at that level:

- **Entry/ Fusion Inhibitors:** This the largest group of products which work by preventing the virus from fusing or entering target cells.
- **Defense Enhancers:** Products which maintain the inherent acidity of the vaginal compartment.
- **Uncertain:** Compounds whose mechanism we don't fully understand; Praneem, an Indian polyherbal preparation, is an interesting example.
- **Membrane Disruptors:** Products that disrupt virus envelope, but also disrupt memalean cell envelope.
- **Replication Inhibitors:** This is a group of essentially HIV drugs which can be used topically to try and prevent transmission. These are drugs which inhibit reverse transcriptase and prevent viral replication.

Reverse Transcriptase (RT) - Inhibitors

Dr. McGowan expanded on the RT-inhibitors. He explained the issues related to this class of drug.

Resistance: 1) What is the relationship between systemic absorption and the development of resistance? 2) Will the risk be altered by the presence or absence of oral combination therapy? 3) Could resistance occur during seroconversion? 4) How should we assess resistance? 5) What are the therapeutic implications?

Pharmacokinetics: What you are doing with Tenofovir gel is delivering the product to a very confined area, so the actual concentrations at the tissue site may be sufficient to avert infection. This is just amplifying the question again of the resistance issues, this issue of the relationship between systemic and local absorption.

RT Combinations: A combination microbicide is being tested in animal studies with macaque monkeys using combinations of CCR5 inhibitors, gp120 fusion inhibitors, and gp41. The findings indicated that the control monkeys all got infected and the group receiving all three drugs was completely protected. The problem is that the levels of drug required to achieve protection would translate into a very expensive product, and this is a recurring theme of microbicide development, the need for effective and safe products that are also economically viable.

Formulation Science

Dr. McGowan explained how the field of microbicides evolved from the contraceptive spermicidal field, and so the products in advanced stages of development are all gels, but it doesn't necessarily have to be so. According to Dr. McGowan, we are moving into an era of much better formulation science. We are generating products and carriers which are being put together on the basis of: stability, rheological properties, absorption, local environment (vagina vs. rectum), and acceptability. We are also moving to a broader range of delivery systems: gels, foams, films, suppositories and rings. It will be necessary to gauge what men and women feel about using these products in real world situations.

Rectal Microbicides

Dr. McGowan explained the importance and rationale for moving microbicide science in this direction:

- Anal intercourse (AI) is the primary risk factor for HIV transmission among MSM.
- The prevalence of AI among the heterosexual population is underappreciated and represents a significant risk for HIV transmission.
- Much AI is unprotected.
- The rectal mucosa is highly vulnerable to HIV infection.
- Based on the N-9 experience, vaginal products may not be suitable for rectal administration.

International epidemiological data show there is significant levels of anal sex in heterosexual couples. In a large study of young adults in the U.S. the prevalence of anal intercourse was between 35-40 percent.

Dr. McGowan discussed a modeling study that simulated putting a rectal microbicide into a bathhouse and found that if a product is 50% effective, or even 30% effective, you will cross the very important line, the R line, which defines epidemic spread. The modeling

suggested that in a high risk situation the use of a microbicide with partial efficacy may actually be advantageous.

The big issue in rectal microbicide development is safety. The future of rectal microbicide development can be viewed in two ways: a specific rectal microbicide product and a product which might be used in both the vagina and anus.

Microbicide Development and the Community

Microbicide development, and any kind of biomedical behavior prevention trials, must have a close and meaningful dialogue with community. Even when you have their support there can be challenges in terms of end points varying.

In closing, Dr. McGowan noted that many of the microbicide trials will begin reporting results as early as 2007, and over the next six years data will be available from six studies. This information will tell us if the science of microbicides is going to work.

To view Dr. McGowan's PowerPoint presentation, please visit the CHIPTS website at: <http://chipts.ucla.edu>.

Microbicide Acceptability and Adherence

Alex Carballo-Diequez, Ph.D.

HIV Centre for Clinical and Behavioral Studies

Columbia University, New York, USA

Dr. Carballo-Diequez discussed the importance and impact of microbicide acceptability and adherence. He discussed normative practices, sex-related behaviors and sexual behaviors that will affect microbicide use.

Highlights of Dr. Carballo-Diequez's presentation:

Microbicides have the potential to prevent HIV transmission when used in the vagina or rectum; however, to be effective people must be able and willing to use them (acceptability) and able to use them correctly and consistently (adherence).

Social scientists have been assessing potential users' opinions on a variety of aspects associated with microbicides: 1) products' physical characteristics, 2) applicator qualities and application methods, 3) products' behavior during use, 4) use with different partner types and partners' attitudes, 5) contextual and situational circumstances of product use, and 6) issues specific for vaginal microbicides (i.e., contraceptive activity, attitudes about female-controlled prevention methods).

Other factors that will affect microbicide use include understanding the normative practices across populations and cultures:

- External and internal vaginal cleaning practices
- Other vaginal or rectal medications or products used
- Access to cleaning facilities

It is also important to consider different sex-related behaviors and sexual behaviors that might affect microbicide use:

- Lubricant use prior to and during sex
- Lubricant use by women for vaginal dryness
- Use of prescribed and non-prescribed sex enhancing drugs
- Means of recreational drug administration (e.g., cocaine inserted rectally)
- Facilities for pre and post coital hygiene
- Power dynamics
- Different types of sexual partnerships
- Serostatus of partners
- Planning for sexual activity
- Sexual site sequencing (e.g., anilingus prior to anal penetration)
- Position during sex
- Expectancy of sexual satisfaction
- Communication around sexual practices
- Different types of sexual activity
- Condom use
- Pregnancy prevention methods

Dr. Carballo-Diequez described the results of a study exploring the acceptability of different volumes of gel inserted rectally among men who have sex with men. Using a surrogate product with escalation that went from 5 ml to 50 ml he found that between 20 – 35 ml were acceptable to participants. What he observed was that as the volume increased, the acceptability decreased – the lower the volume, the more comfortable people felt with it, and also that problems associated with using the gel – such as leakage, soiling and bloating were also reported more frequently as the volume increased.

In a follow up trial with 100 men the 35 ml gel is being compared with a suppository. The study also enrolled 28 women of various ethnic backgrounds who have responded to in-depth interviews about their anal sex practices.

Dr. Carballo-Diequez also examined the issue of rectal douching which can potentially affect use of rectal microbicides. In his study, he found that 60% of participants used enemas prior to sex. Most men used enemas before sex for hygiene reasons. Those who used enemas after sex assumed they offered STI protection.

Current understanding concerning rectal microbicide was summed up as follows:

- Most MSM use rectal lubricants and might use a rectal microbicide gel.
- Gels that are transparent, scent and flavor free are popular.
- Many men have used gels with N-9 and some even continue to use them.
- Education will be needed to address efficacy expectations, questions by users, and the need to counteract negative attitudes about the product.
- Social scientists need to be part of the study design process of microbicide trials (rather than be added on) to consider issues such as pros and cons of: 1) inclusion of people at low risk, or those in monogamous relationships, 2) requirement to use condoms, abstain from douching, or not use sex toys for people whose behavior is not such, and 3) importance of not limiting trial to solo use but including sexual partners.

- Phase 1 trials offer an excellent opportunity for qualitative inquiry.
- Product acceptability is not an inherent, stable attribute of the product, but is affected by contextual circumstances.
- Qualitative studies may contribute to:
 - Increasing the chances of “incidental learning” that may be very important to identify those aspects that facilitate or complicate product use.
 - Identifying instructions or descriptions that were somehow problematic or unclear.
 - Identifying desirable or appealing features of the product as used in the trial that might be instructive for future trials as facilitators of adoption, adherence, and appropriate management (e.g., safe, secure storage and disposal).

To view Dr. Carballo-Diequez PowerPoint presentation, please visit the CHIPTS website at: <http://chipts.ucla.edu>.

Panel Session #2: Pre-Exposure Prophylaxis

The Iniciativa PrEx Study: Safety, Efficacy, Behavior, and Biology

Robert M. Grant, M.D., M.P.H.

Gladstone Institute of Virology and Immunology

University of California, San Francisco, USA

Dr. Grant provided a brief overview of preclinical evaluation of Tenofovir, rationale for pre-exposure prophylaxis (PrEP), and described his PrEP research project in Latin America. Dr. Grant suggested the idea that PrEP can be thought of as a systemic microbicide.

Highlights of Dr. Grant's presentation:

The idea for PrEP is based on pre-clinical evaluation of Tenofovir done with non-human primates. Findings from those studies indicate that:

- Tenofovir was 70%-100% effective against SHIV or SIV
- Emtricitabine + Tenofovir combination was 100% effective after repeated rectal exposures
- Prophylactic activity likely reflects: Long intracellular half-life; activity in macrophages; high penetration into genital tissues

Dr. Grant presented the rationale and significance of PrEP. First, it is used daily, regardless of whether the person has perceived that they had a risk exposure. It can be initiated by women, and in many cases the person taking PrEP does not need to inform their partner. Second, the concept is proven for prevention of malaria (80 to 90% effective), pneumonia (90% effective) and unwanted pregnancy (99% effective). Third, this prevention strategy does not require coordination with risk behavior. In order to be effective, it will require identification of high risk groups, but not specific high-risk acts.

Dr. Grant described his current PrEP trial in Peru which will enroll 1400 high risk men who have sex with men who will be randomized 1 to 1 to receive daily oral PrEP versus a placebo. Participants will be followed for 72 weeks for a whole series of outcomes:

- HIV infection
- Adverse events, particularly renal or liver effects
- Risk behavior and STIs
- Bone mineral density and fat composition
- Adherence to the regimen
- Immune responses that may occur in people who are exposed to HIV during periods of chemoprophylaxis
- If the person becomes infected during the study they will look for:
 - Evidence of drug resistance
 - Viral load
 - Immune responses and CD4 counts.

In addition to his study in Latin America, there are several other PrEP trials being conducted around the world: San Francisco, Atlanta, Ghana, Nigeria, Cameroon,

Botswana and Thailand. These studies are being done with heterosexual men and women, injection drug users and men who have sex with men.

In his study, Dr. Grant is using the combination of Emtricitabine and Tenofovir (Truvada). The choice of this particular regimen was based on the following:

- TDF alone was only partially effective after repeated SIV exposures in monkeys (*Van Rompay et al, Bangkok 2004; Subbarao et al, 12th CROI 2005*)
- Information from other settings indicated that combinations of drugs increase efficacy and decrease resistance risk in treatment settings as well as mother to child transmission
- Addition of FTC does not add substantial safety concerns to TDF alone and FTC + tenofovir was completely protective in 6 out of 6 monkeys

Another important characteristic of this particular study is the inclusion of people with active hepatitis B infection. Hepatitis B is endemic in many of the areas that are also endemic for HIV, namely Africa, the Indian region of Latin America and Asia. As such, it is very relevant to know the safety and efficacy of PrEP in patients who are also infected with hepatitis B virus. This is an issue because the regimen being used to prevent HIV is also known to be active against hepatitis B infection. The question being asked is, is there any therapeutic benefit in these patients? The benefit might include E antigen conversion, but we also have to ask if there is a risk of flare up of hepatitis B when people stop chemoprophylaxis with FTC or TDF.

A challenge in implementing PrEP really starts with challenges in doing the research. A major concern is that optimism about this strategy and the availability of the drug in many settings, especially First World settings, US and Europe, could lead people to think that this is already a proven strategy.

The other challenge for PrEP research is the risk of over-burdening research to the point that the research really can't proceed. There has been some controversy about PrEP trials, some of that controversy has been very useful and productive, and researchers have learned new ways of consulting with the community, better ways of talking with people about new research ideas, and have started to address very important questions about treatment of adverse events in the context of clinical research.

Dr. Grant discussed the significance of the PrEP trials research. We need research to determine appropriate level of required monitoring for individuals using PrEP; whether it is indicated or contraindicated in the setting of hepatitis B; appropriate targeting of PrEP (e.g., only high risk, moderate risk or no one); and whether one or two PrEP agents is optimal for this approach.

He outlined other future questions for future implementation:

- When to start PrEP?
- When to stop PrEP?
- Discontinuous use or use triggered by perceived exposure is appropriate and effective?
- Cost minimization (e.g., minimum protective level of adherence required)?
- Drug costs
- Monitoring costs

- Delivery costs (e.g., paramedicals or medical staff required to deliver this intervention)
- Who pays?
- Optimal counseling

Dr. Grant concluded his presentation with a discussion of a significant issue with PrEP - behavioral disinhibition. As he mentioned, the possibility exists that people will perceive less HIV risk per sexual act and therefore may have more sexual acts. However, there is some encouraging data from the field. In open label studies of post-exposure prophylaxis researchers found that reported risk behavior decreased in the context of the studies.

To view Dr. Grant's PowerPoint presentation, please visit the CHIPTS website at: <http://chipts.ucla.edu>.

Assessing Community and Investigators Needs for Successful Trial Implementation

Pedro Goicochea, MSc, MA

*Asociacion Civil Impacta Salud y Educacion (IMPACTA)
Lima, Peru*

Mr. Goicochea's presentation outlined the need for community engagement in designing a clinical trial for PrEP in a foreign setting.

Highlights of Mr. Goicochea's presentation:

In Peru HIV prevalence is low in the general population. High prevalence exists among MSM with the range anywhere from 3.9 to 6.7 per 100 persons. The explosive spread of HIV among MSM has made Peru a hot spot for HIV clinical trials.

In Peru there has been great success in recruiting participants into studies. From 2002 to 2006 approximately 12,870 people were enrolled in 21 studies and trials. These studies were done with the general population, MSM, women, and people living with HIV and AIDS.

PrEP is a controversial study, and there was concern among local stakeholders about what this study was that was targeting MSM. Limited information existed on the other PrEP trials, such as how these trials were doing and what were the reasons why some of these trials had been stopped. This atmosphere provided a perfect opportunity to do something that had not been done before, and that was a community consultation process.

The community consultation process was basically a way to put the PrEP study protocol out there for the people to read it. Sexual reproductive health and HIV activists had the chance to read the protocol and to make comments in two community forums and to talk directly with investigators about their concerns in order to have the investigators redesign the study. All the concerns raised were answered at the time of the community forum, and then those that were reasonable were included in the new protocol.

In the local agency, Impacta, there is a very large regulatory consultation process for study trials that includes:

- Review of the protocol by community advisory boards from each site
- Review of the protocol by different IRBs or independent ethics committees
- Review by the Ministry of Health and the Peruvian National Institute of Health

For the PrEP study, different approaches were used to assess the needs of the community and the different stakeholders. Using the minutes from the discussions at the community advisory boards, transcripts from the open forum discussions, and focus group discussions, text analysis, discourse analysis, and analyses of focus groups were done using a grounded theory approach to try to understand what were the different demands and needs from different communities and stakeholders. This approach was done prior to implementing any trial in Peru. Issues that surfaced included:

- Coercion – Is monetary compensation coercive? Should compensation even be provided? What amount of monetary compensation becomes coercive?
- Informed consent – Who should do the consenting given the complexity of PrEP (medical doctors or nurses or counselors)?
- Safety and liability – Who will be responsible for adverse events?

From the focus groups, they discovered that among potential participants there existed four different cultures and subcultures of MSM in Peru:

- Buses – MSM that are not out of the closet
- Deschavados – The most effeminate group and the one probably already open to their sexuality
- Fletes and Mostaceros – Commercial sex workers or escorts of Deschavados
- Trans, transgenders or transvestites

The concerns of these different groups of MSM regarding the PrEP trials included:

- Availability of information on HIV and prevention of infection
- Safety of the study medication and adverse events
- Responsibility towards HIV prevention

One important issue that emerged was the responsibility of the gay community towards preventing HIV. Potential participants felt that to be part of the study means to be part of a bigger effort to address the HIV epidemic.

Good bi-directional communication is important between the researchers and the participants along with quality of care at the clinics, and a clear understanding of the aims of the investigation.

To view Mr. Goicochea's PowerPoint presentation, please visit the CHIPTS website at: <http://chipts.ucla.edu>.

Panel Session #3: Male Circumcision

Male Circumcision: A Prevention Method Against HIV in South Africa

Bertran Auvert, M.D., Ph.D.

University of Versailles

Saint Quentin en Yvelines, France

Dr. Auvert provided a brief overview of the correlation between male circumcision (MC) and HIV prevalence and the use of MC as a prevention strategy. He covered the following areas: biomedical evidence, potential impact, acceptability, risks and feasibility.

Highlights of Dr. Auvert's presentation:

Biomedical Evidence

Dr. Auvert presented findings from ecological studies in Africa that showed where MC was greater than 80%, HIV prevalence was less than 6%, and in countries where MC was less than 40%, HIV prevalence was greater than 20%.

Meta-analysis of observational studies on MC indicated that not only in high risk groups, but also in population based studies, circumcised males were less likely to be infected with HIV.

Dr. Auvert discussed findings from his study, "The Orange Farm" trial. In this trial, 3,272 young males 18 to 24 years old were recruited for the study, most of them were already sexually active, and they were randomized into two groups. In one group, circumcision was done at the beginning of the study, and in the second group, circumcision was delayed until the end of 21 month follow up period. In a comparison of outcomes, 40 infections were found in the uncircumcised group versus 28 in the circumcised group. So as a result, the intervention prevented 6 out of 10 potential HIV infections, meaning the protection offered by MC was about 60%. The findings from this trial were comparable to all the other observational studies.

Potential Impact

Dr. Auvert discussed the potential impact of MC on HIV incidence. Recent modeling studies estimated that in the next 10 years, about 2 million new HIV infections could be averted if MC is promoted and is successful in circumcising most of the uncircumcised men in sub-Saharan Africa. Ten years later, 3.7 million new HIV infections could be averted. Dr. Auvert noted that MC is equivalent to an intervention, such as a vaccine or increased condom use that reduces transmission in both directions by 37%. However, for MC to be effective, certain conditions must exist:

- Primarily heterosexual spread of HIV
- MC has to be low
- HIV prevalence has to be high in order for MC to be cost effective.

Acceptability

Is it acceptable? Two thirds of the male population in Africa is already circumcised. There are cultural reasons for being circumcised or not and they will vary from one

country to the next. There are also differences in the age at which circumcision is done (e.g., at birth to age 19). The way circumcision is practiced can also be very different; it can be done by doctors, nurses, general practitioners, or by traditional healers. The cost will also vary.

The results of recent acceptability studies show that in South Africa more than 70% of non-circumcised males stated that they would want to be circumcised if MC were proved to protect against STIs.

Other acceptability studies conducted in Kenya, Uganda, Botswana, Haiti, Tanzania, Zambia, Zimbabwe, reported acceptability rates of 48-85%.

In South Africa, focus group discussions show that MC is still important to many people and is seen as an essential part of the transition into adulthood. Reluctance to be circumcised was mainly related to the possibility of adverse outcomes of circumcision performed in non-medical settings. The cultural importance of MC has weakened over the last century and when it is done it is often done by a medical practitioner. It might be that future MC will be done by a clinician but still maintain its cultural relevance associated with transition into adulthood.

Risks

In the Orange Farm trial circumcision was performed by a general practitioner and the complication rate was low, about 3.8%, with no permanent damage, meaning that it was very safe. A clear limitation with this finding is that MC was done in the context of a trial. If circumcision is done in other ways the rate of complications could be much higher.

Behavioral disinhibition

Another potential risk is a change in sexual behavior associated with MC. An adult being circumcised could feel that they are protected against HIV which is not completely wrong, but they are not completely protected. In the Orange Farm trial there was no difference in condom use or non-spousal sex partners between the circumcised and uncircumcised males. With MC there is the potential for increased risk behaviors. But MC will help in preventing HIV infections, but it is important to be clear with those receiving circumcisions that it provides only partial protection.

Feasibility

Several questions will need to be answered to determine if it is feasible:

1. Are the findings from the other trials in Uganda and Kenya comparable with the Orange Farm trial?
2. What is the effect of adult MC on other STIs?
3. What is the effect of adult MC on male-to-female transmission of HIV? Given that the trials looked at female-to-male transmission.
4. Is it cost-effective?
5. What will be the effectiveness of adult MC in the real world, particularly at the scale of a city:
 - Impact on HIV (short and long term)
 - Uptake of adult MC
 - Uptake of infant MC
 - Sexual behavior change (risk compensation)
 - Impact on condom use

In order for this to work, it will be necessary to develop a new procedure for adult MC that is safe, affordable, simple, and usable by nurses.

Social/Behavioral issues/questions associated with scaling up MC

- Communication about adult and infant MC
- Who will perform circumcisions (doctors, nurses, traditional healers)?
- Who will be the target population for this strategy (all uncircumcised adults, young adults)?
- How can MC be integrated with existing health structures?
- How will MC be integrated with existing prevention strategies?
- How are we going to monitor the effect of this strategy?
- What is the involvement of women?

Dr. Auvert concluded his presentation with the following statement, "I am reasonably optimistic of the potential of MC, at least in Africa, and it is a very rich research area for social, behavioral and biomedical scientists to work together in.

To view Dr. Auvert's PowerPoint presentation, please visit the CHIPTS website at: <http://chipts.ucla.edu>.

Male Circumcision for HIV and STI Prevention in Men and Women

Maria Wawer, M.D., M.H., S.c.

*Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland, USA*

Dr. Wawer provided an overview of how MC is protective in acquiring and transmitting HIV. She also discussed the relationship between MC and female acquisition of HIV and the need to enroll women in clinical trials. Dr. Wawer further discussed issues of surgery and risk and programmatic issues associated with scaling up this intervention.

Highlights of Dr. Wawer's presentation:

Biological plausibility as to why MC might reduce the risk of HIV acquisition and transmission. First, the inner mucosa of the foreskin is incredibly rich in HIV target cells. It has approximately nine times more target cells than the external mucosa of the female genital tract. The intact foreskin is also associated with other infections including genital ulcer disease.

On the mucosal surface of foreskin the amount of keratin is very, very small compared to the external foreskin, and this makes it much more vulnerable to HIV acquisition and also to tears.

In explant culture, in cells grown in Petri dishes, the external surface of the foreskin has almost no infected cells, whereas cells that are taken from inside the foreskin show infected T cells, and HIV bound to Langerhans cells.

The apparent HIV protection afforded by circumcision may be greater in high risk populations than in general populations

Dr. Wawer discussed a real paradox with MC in that it may appear that MC is more protective in highly exposed men than in men who are less exposed to HIV infection. In general populations, out of about ten studies, the risk reduction associated with MC was just over 40%, whereas in high risk populations it was closer to 70%.

A similar finding was noted for Dr. Wawer's Rakai data, which included HIV negative men who were married to HIV positive women. If the men were circumcised, there were no transmissions to the men, compared to high levels of transmission from women to uncircumcised men, particularly at higher female viral load.

Why might this paradox exist? It is possible that once you remove the foreskin there is only a very small mucosal surface left, so the male is exposed to low doses of HIV, and if the low doses occur repeatedly, it could be analogous to the reduced infection in highly exposed but persistent seronegative commercial sex workers. They are getting frequent low doses and there might be a potential induced mucosal immunity.

This would be a rather difficult message to deal with if MC does become a program, because you don't want to tell people the more highly exposed you are, the more protective it is going to be.

Male circumcision and female acquisition of HIV infection

Dr. Wawer reported on findings from her Rakai study. If the male was circumcised, the transmission from the male to female was reduced by about 60%. If the male viral load was below 50,000 copies, and the male was circumcised, there were no transmissions. If the male was uncircumcised the transmission was almost 10 per 100 person years. If the male viral load was above 50,000 copies, then whether the male was circumcised or not, there wasn't any protective effect.

There are limits to these observational studies. Men get circumcised because they belong to a particular religion or tribal group or social cultural group, and there may be correlated differences in behavior: Religion may be correlated with lower risk behaviors, less alcohol use, genital hygiene, etc.; traditional/tribal customs may be associated with behavioral differences or puberty rituals; medical indications may be correlated with higher risk behaviors.

Clinical trials

Dr. Wawer described three MC trials: the one in South Africa that had a highly positive and protective effect, and two ongoing ones in Kenya and Rakai. All of them had similar designs; they enrolled HIV negative uncircumcised men who were randomized to immediate circumcision or circumcision delayed for approximately two years with end points of HIV incidence, safety, behavioral disinhibition and effects on other sexually transmitted infections.

There are differences in the trials; one is semi-urban, one rural, one urban; one is community based, the others clinic based; the baseline circumcision rates are different; and the baseline incidence of HIV is different; the age range was also different. So the

trials were looking at this procedure in different populations. The surgical procedures used in the three trials were also different: clamp/cut or sleeve.

The results of the first trial (i.e. Orange Farm trial) were consistent with observational studies, but there are caveats if you only go with one trial. Trials stopped early may over-estimate efficacy, there is also the need to assess the longer term effects of circumcision, and there is also the need to assess circumcision in different populations. There is a risk when trying to base major policy on only one trial. So the public health response has been that the completion of the two trials, that is Uganda and Kenya, is needed before finalizing policies.

The Rakai trials also include HIV positive men and women. So the question is: Why include HIV positive men in these trials? The goals of the study are to:

- Determine safety of circumcision in HIV+ men: If circumcision is safe in these men (AEs, healing) future programs will not need to screen them out.
- Measure STI effects of MC in HIV+ men: If circumcision is beneficial in HIV+ men, future circumcision programs may promote circumcision for these men.
- Reduce stigmatization: Less likely HIV+ men will seek unsafe procedures.
- Potentially reduce behavioral disinhibition: HIV-negative men don't get "proof of negative status"

Why include women in these trials? The goals of the study are to assess:

- Safety or potential benefits of circumcision for women: If an HIV+ man becomes circumcised, is he more or less likely to transmit HIV to female partners? Are circumcised men (whether HIV-negative or HIV-positive) less likely to transmit other STIs to women? Determine factors influencing potential risk or benefits.
- Behaviors in couples after male circumcision.
- Whether program cost effectiveness will be higher if women also benefit and the strategy can be used in populations with lower HIV prevalence.

In the Gates Funded trial of male circumcision they are looking at HIV transmission to women.

- Population
 - ~ 800 HIV+ men, ages 15-49
- ~ 4300 women in the community; linked partnerships to men in the NIH and Gates trials
- Primary Endpoints
 - Safety in HIV+ men
 - STD acquisition in men and women
 - HIV transmission to women (safety and efficacy)
 - Behavioral effects in participants and partners

The Gates Funded trial and the trial follow up will end in 2008. The study is paying close attention to safety of equipment, autoclaving equipment, etc. which is something that all programs will have to think of. A program will not want to have equipment which is insufficiently sterilized and might itself increase risk. This study was stopped by its DSMB.

With respect to safety in the Rakai study:

- Median time to certified wound healing 28 days (same in HIV-negative and HIV positive men)

- Median time to resumption of sex 43 days
- Only 11% of men resumed sex before wound healing was certified as complete
- Frequency of all moderate or severe complications requiring treatment ~ 2-4% in the three trials
- Infections, bleeding, hematoma, wound dehiscence, inadequate skin removal
- Complication rates and wound healing are equivalent in HIV+ and HIV-negative men

There were no signs of behavioral disinhibition among participants in the Rakai trial. Instead, increased condom use was shown after circumcision.

Acceptability in Rakai

Of the general male population in the 50 villages included in the study, 48% agreed to be in the trial. So even before the results on whether it does or does not reduce HIV, it is highly acceptable in a population that is not traditionally circumcised.

In relation modeling conducted by the investigators, it was shown that MC might reduce HIV acquisition if it only benefits males, but if females also benefit, the effects are much more profound.

If behavioral disinhibition occurs, modeling shows that the positive effects of MC would be undone. Even if circumcision proves to be effective it will be necessary to continue to work on promoting condoms, safe sex behaviors, etc.

The number of circumcisions needed to prevent one incident HIV infection over a cumulative 10 year period, if circumcision is 50% effective, and if it is only effective in men, is 46; if it is also effective in women, the number goes down to 22.

Issues of surgery and risk

You have to have people who know what they are doing. It would be more advantageous to have a well trained nurse who does these things day in and day out, than a surgeon who does it once a month.

Programmatic issues – the scale up

The question is: Will we need specialized surgical centers at least for training and to provide a cadre of truly qualified practitioners who can do supervision, but also to make sure that practitioners get enough ongoing practice?

- Scale up to provide safe adult circumcision (training, equipment, supplies/medications etc.)
- Specialized surgical centers to maximize quality of surgery and postoperative care
- Discourage traditional practitioners or poorly trained private practitioners
- Provide neonatal circumcision?
- Prevent behavioral disinhibition and maintain HIV prevention efforts

Summary and Conclusions

MC could have a major impact on the HIV epidemic, especially if protective in both sexes. Other potential benefits include decreased STIs in both sexes. Behavioral disinhibition could offset benefits such that intensive risk reduction and integration with other preventive programs are essential.

To view Dr. Wawer's PowerPoint presentation, please visit the CHIPTS website at:
<http://chipts.ucla.edu>.

Panel Session #4: Regional Mobilization

HIV Prevention: Behavioral and Biomedical Interventions in the U.S.

Kevin Fenton, M.D., Ph.D.

*Director, National Center for HIV, STD, and TB Prevention
Atlanta, Georgia, USA*

Dr. Fenton provided an overview of the Centers for Disease Control and Prevention's (CDC) comprehensive HIV prevention program in the United States. This included a description of the strategic initiatives in which all prevention interventions and activities are housed. He then focused on evidence-based behavioral interventions effective in HIV prevention. He concluded with some of the biomedical interventions under development and evaluation by the CDC.

Highlights of Dr. Fenton's presentation:

HIV prevention means using the best strategy for reducing the human and economic toll of HIV. To have the largest impact, CDC uses a comprehensive approach to HIV prevention, incorporating surveillance, research, prevention interventions, and evaluation.

CDC conducts extensive biomedical and behavioral research to better understand the complex factors that lead to HIV infection and to identify effective approaches to prevent HIV, such as:

- Behavioral interventions shown to be effective through randomized control trials have been implemented and disseminated for use with high risk populations through the CDC's Diffusion of Effective Behavioral Interventions Project (DEBI), and the Replicating Effective Programs Project (REP)
- Biomedical interventions research supported by CDC includes microbicides, vaccines and oral chemoprophylaxis studies

Context of HIV prevention in the United States

There have been some successes in HIV prevention efforts; however, tremendous challenges remain. Successes include:

- Steady decline in perinatal HIV transmission
- Reduced risk behaviors among youth
- Declines of HIV among injecting drug users
- Stable HIV incidence with increasing prevalence

The strategic framework in which all CDC prevention efforts are being delivered is known as the Advancing HIV Prevention (AHP) new strategies for a changing epidemic; this strategy was launched in 2002. AHP emphasizes the use of proven public health approaches to reduce incidence and the spread of disease:

- Make HIV testing a routine part of medical care
- Implementing new models for diagnosing HIV infections outside of medical settings

- Preventing new infections by working with persons diagnosed with HIV and their partners
- Further decreasing perinatal HIV transmission

As part of the AHP, CDC has funded a number of demonstration projects to identify new models and new prevention interventions that could be applied and scaled up. One example is the CDC project on social networks, or social network strategies. In this project nine community based organizations use social networks to encourage HIV counseling, testing and referral services.

The DEBI Project is another prevention success of the CDC. This involves diffusing effective behavioral interventions for primary and secondary prevention either with individuals, small groups or communities. Through the DEBI program, training and ongoing technical assistance is provided to state and community organizations using evidence based approaches. These interventions help to ensure that persons at greatest risk of HIV transmission or acquisition are able to obtain intensive support to reduce risk behaviors and to adopt prevention strategies for their health and the health of their partners. Examples of DEBI interventions include:

- RAPP
- Many Men, Many Voices
- Popular Opinion Leader
- Healthy Relationships
- Street Smart
- Sista
- Community Promise
- Empowerment
- Safety Counts

The CDC is supporting the development of new biomedical interventions as tools to add to the arsenal for fighting the epidemic. Biomedical research activities being sponsored by CDC include:

- Evaluating pharmaceutical interventions to prevent HIV infection
- Supporting vaccine development
- Evaluating the effectiveness of products such as microbicides
- Evaluating new diagnostic tests and testing algorithms

CDC is sponsoring three clinical trials of the anti-retroviral drug Tenofovir. The trials are designed to answer important questions about the safety and efficacy of Tenofovir as a daily oral HIV preventative agent (PrEP).

- Thailand: 1,600 injection drug users
Safety and efficacy of tenofovir (Phase II/III)
- Botswana: 1,200 sexually active young men and women
Safety and efficacy of tenofovir/emtricitabine (Truvada) (Phase II/III)
- US: 400 men who have sex with men
Extended safety trial of tenofovir (Phase II)

CDC is also collaborating with a number of other agencies as a part of the Partnership for AIDS Vaccine Evaluation or PAVE.

- CDC is working with local officials and scientists in a number of countries around the world including Cameroon, Central Africa and Kenya, to prepare study sites and populations for eventual HIV vaccine trials
- CDC epidemiologists are also supporting minority scientists domestically in conducting behavioral studies which were related to vaccine trials and research
- CDC laboratories are conducting a number of new generation studies looking at animal challenge experiments to better evaluate the potential protection of a brand new vaccine, Candidex

CDC is evaluating the safety and acceptability of the use of UC-781 microbicide in studies being conducted in three locations: Thailand, Botswana and the U.S.

One area that biomedical research has certainly had a tremendous impact in the U.S. is in improved HIV testing technologies. Widespread availability and use of diagnostic and screening tests for HIV have really helped to ensure the safety of the nation's blood supply, and this certainly has been a prevention success.

In summary,

- Behavioral interventions are a critical element of HIV prevention programs in the U.S.
- Biomedical interventions offer promise for the future
- All tools are needed to combat the HIV epidemic in the U.S.
- Prevention remains key

To view Dr. Fenton's PowerPoint presentation, please visit the CHIPTS website at: <http://chipts.ucla.edu>.

HIV/AIDS: A Special Infectious Disease

Zunyou Wu, M.D., Ph.D.

Director, National Center for AIDS/STD Control and Prevention

Chinese Center for Disease Control and Prevention

Beijing, China

Dr. Wu provided an overview of China's efforts to increase HIV testing nationally in an effort to reduce the incidence of HIV infections.

Highlights of Dr. Wu's presentation:

Over the past 25 years China has made a concerted effort to control its HIV/AIDS epidemic; however, because HIV/AIDS is treated differently than other diseases the focus on HIV/AIDS as a communicable disease has been lost. The emphasis has been on protecting the rights of HIV infected individuals, with little attention given to the rights of uninfected individuals. It has been forgotten that HIV/AIDS is a communicable disease.

Emphasis has been on the right of people to choose not to be tested. People becoming infected do not know they are infected. Individuals who are infected but unaware of their status may continue to spread the virus.

HIV testing began with anonymous testing. Anonymous testing provides HIV prevalence, but no information on infected individuals. This information has limited utility in controlling the epidemic. It is useful for developing public education campaigns. However, the assumption behind these campaigns is that people behave rationally and will take action to change their behaviors. This strategy has had little impact on the epidemic. By doing anonymous testing, people who test positive may not return for their results and may continue to engage in behaviors that may transmit the virus to others. With this strategy we also lose the opportunity to provide treatment to positive individuals.

The second strategy for testing is confidential testing. It provides HIV prevalence, but also allows us to give results to people who get tested. Based on test results, specific counseling and medical services can be provided. This will have a tremendous impact on individual risk behaviors that could help reduce HIV transmission and prolong the life of infected individuals.

Need to utilize public health principles to stop the spread of HIV/AIDS:

- Early identification of individuals infected with HIV
- Provide individuals with counseling, skills and tools (e.g., condoms, clean needles, methadone maintenance programs) so that they do not transmit the virus
- Provide HIV positive individuals with treatment and medical care

In China, there are a large number of people infected, but few are being tested. Among those who have been tested, there is an even smaller proportion that is currently in medical care. One of the major tasks for public health is to try to increase the proportion of people being tested and increase the proportion of HIV positive individuals receiving medical care.

From 2004 to 2005 the Chinese Government launched a major HIV testing campaign.

As part of the campaign, 1,973 voluntary counseling and testing (VCT) sites were established in the 31 mainland provinces. The results of this campaign were an increase in the percentages of infected people identified. Prior to the campaign only 8% of infected individuals were identified. After the campaign, 22% of infected individuals were identified.

The campaign increased the number of people receiving free treatment and also helped reduce transmission. An additional benefit of the campaign was identifying 12,259 discordant couples.

The Chinese government also developed a monitoring system called “Real Time Reporting System.”

Each HIV infected individual is recorded onto a national database website. On average, about 200 new infections are registered each day. By using this system the government can tabulate the number of people being infected, in which region, and by what mode.

A concern among many was whether the testing campaign violated human rights.

The government is committed to protecting the rights of people infected with HIV/AIDS. On March 1st, the government passed a special law to help in controlling the AIDS epidemic.

The law protects the ethical rights of people living with HIV and AIDS patients and their relatives. It includes the right to marry, employment, medical care and education. The law states that no institution or individual shall discriminate against people living with HIV/AIDS and their relatives.

Dr. Wu described the Chinese government's new strategy for HIV prevention which includes:

- Testing as an entry point for prevention and treatment
- Scaling up effective prevention measures that include condom promotion, needle exchange programs, methadone maintenance programs
- Free access to treatment

In terms of harm reduction, the methadone maintenance program reduces drug use, drug related crime and drug related AIDS infections. It improves the quality of life of drug users, and that is consistent with the policy of the Chinese government, which is to develop a harmonized society. It also shrinks the heroin market and reduces the number of new drug users, and therefore, should be used as much as possible.

The Chinese government established a new action plan that states that by 2010 we will limit the number of people living with HIV to no more than 1.5 million.

To view Dr. Wu's PowerPoint presentation, please visit the CHIPTS website at: <http://chipts.ucla.edu>.

Intersections of Socio-Behavioral Research and Biomedical Strategies of HIV Prevention in Tanzania

Jessie Mbwambo, M.D.

*Muhimbili University College of Health Sciences
Dar Es Salaam, Tanzania, E.A.*

Dr. Mbwambo discussed the rationale for the intersection of social/behavioral and biomedical strategies for HIV prevention in Tanzania. She described the current situation in Tanzania as well putting forth questions that need to be addressed about the current situation in order to facilitate implementation of new interventions.

Highlights of Dr. Mbwambo's presentation:

Now, more than any other time in the course of the HIV pandemic, there are more interventions available to fight HIV. New biomedical interventions are emerging at a time when social/behavioral and biomedical scientists have not been talking to each other enough. We need to investigate the intersection of social/behavioral and biomedical

strategies so that we are prepared to address issues arising from these new interventions.

Dr. Mbwambo described the case of Tanzania

Tanzania is in a similar situation as the rest of the world. Persons from different disciplines are not communicating with each other even though they are all working with individuals and communities that have different biological, psychological and social needs. Because of this lack of a clear understanding of the people and communities, there has been limited uptake of interventions, as well as little adherence to those interventions that are implemented. In addition, some interventions are difficult to research and implement because of existing barriers.

Dr. Mbwambo posed several questions related to development of new interventions.

Where does the HIV decision making power lie in the country (who, where and why)?

Are there champions for the cause?

What are the issues related to product entry into the country?

What are the regulatory issues associated with conducting research on a product in country?

Is there a clear understanding of the intervention (what is its effectiveness, at what level is it acceptable to policy makers, 60% vs. 100% effectiveness)?

What is the stigma associated with the intervention?

How does the gender of the person accessing the intervention impact the perception of their risk?

Are there resources available to scale up, and who is responsible for sustaining a successful HIV intervention?

Dr. Mbwambo discussed some of the issues that might arise with implementing microbicides, PrEP and male circumcision in Tanzania or other parts of Africa.

Microbicides

- Microbicides will be a female initiated HIV prevention product.
- It is important not to repeat the problems that occurred with the female condom and PMTCT (e.g., where and what is male involvement?).
- Microbicides will require having a “champion” for the intervention to increase their social acceptability. Most countries do not have champions for a cause so medical orientation prevails.
- Implementation will require social/behavioral and biomedical investigators working together.
- If a microbicide is effective, it will need rapid scale up through multiple channels.

- The product should not be costly in order to ensure sustainability after trials are completed.
- We also need to have a clear understanding of why women will use or not use the product.

PrEP

- As a product offered to people, there will be issues to address as part of the clinical trials, as well as issues associated with introducing PrEP in a resource-limited country.
- In addition, issues of concern include whether HIV risk behaviors will increase because people feel protected by PrEP.
- Other concerns include what it will mean if effectiveness of PrEP is not 100%.

Male Circumcision

- Cultural issues exist for and against male circumcision in Tanzania.
- To what extent will the positive results of MC for HIV prevention be taken up by male populations from uncircumcised communities?
- What additional social/behavioral research needs to be done to ensure that uptake of MC can occur without offending cultural beliefs of persons?

In closing, Dr. Mbwambo suggested that:

No one HIV preventive intervention will be adequate without a thorough understanding of the psychosocial milieu of individuals or a community.

Understanding a country's HIV decision making process is critical to introducing and maintaining HIV preventive and treatment strategies.

Champions need to be identified and their understanding of the intervention nurtured for improved uptake of the intervention.

Mechanisms for scaling up and sustaining the intervention post research and donor support is critical.

Monitoring adherence to the intervention needs to be an ongoing process (Research or Targeted Program Evaluation –TPE)

To view Dr. Mbwambo's PowerPoint presentation, please visit the CHIPTS website at: <http://chipts.ucla.edu>.

RECOMMENDATIONS

Where do we go from here...

From the symposium presentations, we were able to identify a number of issues, challenges, questions, recommendations and suggestions that will help advance our efforts in the development and implementation of biomedical HIV prevention strategies. A primary recommendation of the symposium presenters is the need for more collaboration between social-behavioral and biomedical HIV researchers in order to effectively develop and implement biomedical HIV prevention strategies. Other important recommendations and considerations from the symposium include:

Conducting Clinical Trials:

Community engagement: Implementing clinical trials must begin with an open dialogue with the community. The study should be designed in partnership with community stakeholders in order to avoid future problems and to conduct ethically responsible research. Involving communities can improve the process of clinical research by ensuring that the research is designed appropriately for the populations that will be involved in the study (e.g., appropriate outreach materials, information needed, convenience of participating in the trial, etc.). It is also important for researchers to know and understand where the decision-making power lies in a country in order to know who to approach about implementing a clinical trial.

Community education: Educating the public about biomedical HIV prevention research is the first step to gaining community support and involvement. It is important that communities or groups most impacted by HIV are aware of these research efforts and the potential public health benefit they may hopefully offer one day. In order to encourage individuals to participate in clinical trials, they must have information about why this type of research is important for them and their community, how the research study will be conducted, and the risks and benefits of participating in the research study.

Adverse events: The opposition to some of the PrEP clinical trials brought awareness to the importance of community engagement early on in the process and the need to address questions about treatment of adverse events in the context of clinical trials, particularly in resource-poor settings. Procedures for addressing potential adverse events must be made clear before a trial is implemented.

Target populations: It is important that clinical trials are representative of the ultimate end users of prospective biomedical prevention strategies.

Inclusion of partners: The question is still being debated on the necessity of including partners in studies of sex-related prevention products. On one hand, it will be important to get information about what partners think of the products being used by the partner. On the other hand, there is the issue of social harm; for example, women should be allowed to enroll in microbicide trials without partner acceptance.

Implementing Biomedical HIV Prevention Strategies:

Public education: Public education will need to be an integral component in the implementation and scaling up of any biomedical prevention strategy. During the

implementation process, consumers are likely to have higher expectations from any new biomedical prevention strategy than can be delivered, particularly with first generation products (e.g., microbicides, diaphragms). As such, it will be important that consumers understand the level of protection provided by a particular product. It is also important to address any questions consumers have regarding use of a product. In addition, appropriate public education can help prevent negative attitudes about a product that may deter its uptake.

Comprehensive prevention strategy: Given that biomedical innovations will have different levels of efficacy and none is likely to be 100% effective in protecting someone from HIV, these innovations will need to be provided in combination with risk reduction counseling and barrier methods such as condoms. As new methods for HIV prevention become available, it will be important to think about what a comprehensive strategy will look like. How will biomedical innovations be integrated into existing prevention strategies? Will it be different depending on the setting? Will it be different depending on the methods available in a particular setting? How will the different methods affect what is included in a comprehensive approach to HIV prevention?

Communicating partial protection: Most biomedical innovations will only offer partial protection against HIV infection. As such, it will be necessary to find appropriate and effective ways to communicate this limitation when disseminating products for use by at-risk populations.

Optimal counseling: No matter what the intervention, individuals will need to be counseled regarding its use. What is the optimal counseling for these types of interventions?

Interventions provided in tandem with new technologies: Interventions designed specifically around these biomedical technologies may be needed to ensure appropriate use, adherence and prevent behavioral disinhibition.

Feasibility: An innovation may be effective, but is it feasible? How will it be administered? Is the intervention cost-effective?

Cost: Cost will be a factor when implementing any biomedical innovation. A series of questions regarding cost will need to be addressed: Who will pay for the innovation? How might we minimize the cost of delivering the intervention? The bigger question to be answered is whether the innovation is cost effective and under what circumstances.

Delivery: Each innovation carries with it different requirements for delivery and/or implementation in different settings and with different populations. For example, PrEP is a prescription drug which suggests that only clinicians will be able to administer this method. Or, will other medical personnel be allowed to administer the intervention? A related example is male circumcision, which requires trained clinicians to perform the procedure properly. Or, will it be performed by other medical personnel, such as nurses? In contrast, a more simple technology such as microbicides may be delivered over the counter so that any community provider could potentially offer it to their clients.

Infrastructure and training: Some biomedical interventions will require a certain amount of infrastructure to be in place in order to be implemented. This may be particularly difficult to accomplish in some resource-poor settings. For example, male

circumcision may require clinical facilities and trained medical personnel to be implemented. There may need to be specialized surgical centers, at least for training, and to provide a cadre of truly qualified practitioners who can do supervision, but also to make sure that practitioners get enough ongoing practice to ensure that the procedure is done correctly.

Target population: It will be important to determine the appropriate target population for any new biomedical intervention. Clinical trials will help in determining what populations to target with each of these innovations. In some cases, it may be that the biomedical innovation is most beneficial with very high risk populations, and in some cases it may also be appropriate with moderate risk groups. Some innovations will be targeted to only men and some to only women and others to both genders. It will be essential to figure out how to target a particular strategy to the specific groups that would benefit most from the innovation. Another question to be addressed is whether these innovations will be available to HIV negative and positive individuals, or only negatives, and what might be the impact of excluding certain groups?

The Role of Social-Behavioral Scientists in Development and Implementation of Biomedical HIV Prevention Strategies:

Early participation: Social-behavioral scientists should be part of a study design for a clinical trial from the very beginning and not be added on during phase 3 of a study. An investigation of the social and behavioral issues associated with a biomedical intervention should begin during the clinical trial and not after its completion.

Qualitative inquiries: Phase 1 safety trials offer an excellent opportunity to have in-depth discussions with participants about using the product that can influence future studies. Qualitative studies may:

- Increase the chances of “incidental learning” that may be very important to identifying those aspects of a product that facilitate or complicate its use.
- Provide an opportunity to identify instructions or descriptions of products that were somehow problematic or unclear.
- Help to identify desirable or appealing features of a product as used in the trial that might be instructive for future trials as facilitators of adoption, adherent use, and appropriate management (e.g., safe, secure storage and disposal).

Social, cultural and religious influences: Social, cultural and religious factors can influence acceptability and adoption by individuals and communities of some biomedical prevention strategies. It is important to understand the influence of these factors and address them as part of any implementation or scaling up program. Clinical trials offer a unique opportunity to conduct an initial investigation of the social, cultural and religious factors that can impact implementation and use of a biomedical innovation.

Acceptability Studies: A biomedical prevention strategy cannot be effective in preventing HIV infection if it is not acceptable to its intended audience. Delaying exploring acceptability until later stages of or after a trial may mean missing things that will interfere with the ultimate success of a particular product or strategy. Product acceptability is not an inherent, stable attribute of a product. It will be affected by contextual circumstances related to product use. Acceptability studies should be conducted in conjunction with clinical trials and with the intended end-users of products.

Adherence: Consistent and correct use of biomedical strategies is necessary for effectiveness. Understanding and addressing adherence of these biomedical strategies will be an important part of implementation and delivery.

Behavioral disinhibition (risk compensation): A significant issue that may arise with the implementation of any new biomedical prevention strategy is behavioral disinhibition – increases in risky behavior resulting from decreases in perceived risk. It is possible that people using a biomedical prevention method may perceive less HIV risk and engage in unprotected sex or even more sexual acts. Any increase in sexual risk associated with a biomedical innovation could undermine its potential benefit in controlling the pandemic. To address the possibility of behavioral disinhibition, it will be important to plan ahead. First, it will be necessary to manage optimism about these innovations in preventing HIV by communicating to potential consumers that they will not eliminate the risk of HIV infection. Second, it will be necessary to continue to stress the importance and priority of safer sexual behaviors as effective means of protecting oneself against HIV infection.

Stigma: Anticipating and addressing stigma that may be associated or become associated with new biomedical interventions. For example, with gender-specific interventions such as microbicides, if a woman uses microbicides, what does that tell her partner about her HIV risk? What might be the stigma attached to adopting certain biomedical interventions? How do we address this type of stigma?

Monitoring impact: How will we monitor or evaluate the impact or effect of new biomedical strategies in the real world?

References

Sawires SS, Dwarkin SL, Fiamma A, Peacock D, Szekeres G, & Coates TJ. (2007). Male circumcision and HIV/AIDS: Challenges and opportunities. *Lancet*, 369, 708-13.

Stolte IG, Dukers NHYM, Geskus RB, Coutinho RA, de Wit JBF. (2004). Homosexual men change to risk sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study. *AIDS*, 18, 303-9.